PLAINTIFF'S EXHIBIT
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Exposure to asbestos in various industries and occupations has been associated with three major lesions involving the intra-thoracic organs. The first to be described, asbestosis, is a form of interstitial pulmonary fibrosis, and it has been shown to be dose-related in terms of measured dust concentrations in the workplace and duration of exposure. Lung cancer in heavily exposed workers in industries such as insulation, construction, ship-building and asbestos textiles has been ~~shown to exist~~ adequately documented and related to asbestos exposure. Asbestos workers who smoke cigarettes appear to have a ~~ten~~ 90 times greater chance of dying from lung cancer than non-smoking non-asbestos exposed persons. ~~Non-smoking asbestos workers although the latter group have an eight times greater chance than non-smoking non-asbestos exposed persons.~~ (1) The third major lesion to be associated with asbestos exposure is diffuse malignant mesothelioma of the pleura or peritoneum. Unlike asbestosis and lung cancer, this rare tumour has been ~~less adaptable~~ more difficult to characterize in terms of dose-response and pathologic features. This malignant tumour may also involve the peritoneum. (2) ~~and testes.~~

Less clear cut associations have been described by some observers between asbestos exposure and cancers involving the gastro-intestinal tract (3,4) and cancer in other organs such as the larynx (5) or renal ~~sexual~~ organs. (6) Cancer of the ovary in women has been ascribed to asbestos exposure (7) but there is some doubt as to the ~~difference~~ possibility of differentiating it from peritoneal mesothelioma in the studies published thus far. (8)

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Because of its widespread use in many industries during the past 50 years, up until very recent times, millions of persons have been exposed in various ways to various varieties of asbestos.(9) Asbestos fibers are ubiquitous in the earths crust, waters and atmosphere and have been there since time immemorial. The commercial exploitation of asbestos is thought by some to have added to the normal background of fibers in the ambient air or in water supplies and there has been great concern in recent years about a possible public health risk occurring as a result.(10) There is no data available at present to substantiate or finally refute this fear. The only positive evidence of non-occupational asbestos exposure resulting in demonstrable effects in humans is derived from studies showing :-

(a) the development of hyaline or calcified pleural plaques of a benign nature in certain populations living in the proximity of mines(11) or tailing soils(12) rich in asbestiform minerals, and (b) from the demonstration in retrospective epidemiologic studies of an association between living in the immediate vicinity of asbestos factories(13) or having domestic contact with asbestos workers(14) and the development of malignant mesothelioma. The number of cases of malignant mesothelioma attributable to neighborhood exposure or domestic contact as reported in the world literature is small.(15) The presence of asbestos fibers in water, beverages, drugs and the ambient air has not been adequately correlated with disease in the general population by most observers.

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The incidence of a signal rare tumors such as malignant mesothelioma can be used in population studies designed to investigate the role of asbestos exposure. In all published series of mesothelioma there is a small proportion of cases where exposure to asbestos cannot be conclusively found, but the size of this proportion varies and to some extent may depend upon the care with which the exposure evidence is gathered and the quality of data available for interpretation.(16)

Difficulties in determining whether a case of malignant mesothelioma has occurred as a result of asbestos exposure are caused by factors involved in the natural history of the disease. Although some researchers believe that they have established evidence confirming that this tumor is dose-related,(17) it is widely held that much lower exposure levels than those associated with asbestosis or lung cancer are capable of leading to mesothelioma development.(18) The exposure to asbestos may be minimal in terms of duration, although not necessarily in terms of dust concentrations, and if not a regular daily occurrence during the course of employment or in the course of normal daily events, may easily be forgotten by the patient. The long lapsed period between first exposure and recognition of the disease, commonly 20-50 years, serves to compound this "memory factor". Some of the cases described with no known exposure may fall into this category. It is often very time-consuming and difficult to obtain a complete history of exposure to asbestos, at work and elsewhere, covering an individual's

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lifespan, and it may be equally difficult if not impossible to exclude the possibility of such exposure. Bearing in mind the great difficulties experienced in tracking down occupational exposure to asbestos in certain jobs, the task of attempting to do so in individuals whose work histories are non-indicative is immense and many investigators have not even attempted to do so. This may result in associations being overlooked or a more casual exposure incriminated instead of a more likely one which has been forgotten. ~~or overlooked~~. In these studies using case-control methods the control groups used have not always been appropriate.(19) Another problem encountered in the attempt to isolate causative factors in the development of malignant mesothelioma is the difference in biological effects associated with the different fiber varieties.(20) Crocidolite asbestos from certain regions appears to be most likely to produce this disease, whereas chrysotile is least likely to do so and amosite (cummingtonite-grunerite) holds a doubtful intermediary position. The possibility that all cases of mesothelioma may not be asbestos-related must not be overlooked and recent studies in Turkey have apparently reinforced this concept with the finding that ~~asbestos~~ calcified pleural plaques, chronic fibrosing pleurisy and malignant pleural mesothelioma are endemic in certain villages without asbestos deposits in the soil,(21) ~~where asbestos is not used in the home daily life~~ occupationally. Fibrous erionite zeolite was discovered to be present in the region and it is suspected by some as the etiologic agent.(22) ~~A marked feature of the asbestos-relate~~ It is of (~~the~~) considerable interest to note that a geographic clustering of asbestos-related mesotheliomas has been described mainly

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and aluminum oxide the proportion of fibers with diameters between 0.5 and 2.5 micrometers and lengths 10-80 microns are most dangerous.(26) In experiments using only glass fibers it has been shown that the ~~largest~~ highest incidence of tumors occurred with ~~fibers up to~~ fibers less than or including 1.5 microns in diameter, including those less than 0.25 micrometers in diameter, and with fibers up to lengths greater than 8 micrometers.(27) In the study of mesothelioma cases it is seldom possible to reconstruct exposure histories with the degree of accuracy required to confirm these ~~findings for~~ effects observed in experimental animals, but attention should be paid to determination of fiber varieties (~~many presently~~) which could have been present in the patients' environment.

~~For~~ The reported frequency of mesothelioma in Connecticut has substantially increased in the late 1950's and has continued to increase steadily since that time.(28) The geographic distribution of cases recorded in the Connecticut Tumor Registry reveals a clustering in dense urban areas.(29) In addition to ~~Other~~ descriptive ~~from many~~ deficiencies in the data for the cases studied, such as lack of occupational histories, the possibility of ~~errors~~ diagnostic errors is very real. ~~(A discriminant function analysis of cases of malignant pleural disease~~ pleural mesothelioma and other pleural) It is generally agreed that the diagnosis of mesothelioma can only be made with certainty after examining tissue from the tumor.(30) The diagnosis of mesothelioma during life, even when "adequate" biopsy material is available may still be difficult to make. Primary tumors in other organs may metastasize to the pleura and be difficult to distinguish from mesothelioma. Many pathologists do not agree with current

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diagnostic criteria and this is evidenced by a number of cases not accepted after review by mesothelioma panels.[30,31] The histology of mesothelioma is variable and the tumor may exhibit marked pleomorphism.[32] If only epithelial cells are seen the tumor may be confused with an adenocarcinoma. Certain adenocarcinomas may involve pleural or peritoneal surfaces and simulate mesotheliomas. A necropsy on a case of pleural mesothelioma may take three or four times as long to perform as do most other cases. Whitwell thinks that inadequacies in some post-mortem reports on cases of mesothelioma reflect the exhaustion of the pathologists after their exertions.[33]

There are many indications that the increased incidence of mesothelioma is real but the ability to discriminate readily between false positives (other tumors diagnosed as mesothelioma) and false negatives (cases incorrectly recorded as having other tumors by the Tumor Registry) due to diagnostic errors is lacking at present. [illegible]

~~Another problem has been recognized. Another problem has been identified which should be borne in mind. There is general~~ ~~The lines between localized and diffuse mesothelioma are not always clear cut and the separation of benign from malignant is not always or readily apparent as stated~~ It has been suggested that this increased incidence can be attributed to the tremendous growth of the asbestos industry in the U.S. during and after World War II.[34] In view of the long lapsed period for the development of mesothelioma a continued rise in incidence until at least the end of this century is

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in areas where large quantities of amphibole fibers (crocidolite and amosite) were used. (23)

The precise mechanisms whereby asbestos produces its ~~malignant~~ carcinogenic effects are not known but it has been postulated that is believed that the ability of asbestos fibers to penetrate the to the depths of the lungs and reach the pleural surfaces is dependent upon their shape and size. (24) The diameter of a fiber determines its capacity to remain airborne and the number of fibers per unit mass is greater the finer the fibers are. It is thus obvious that fiber diameter determines the number of fibers inhaled. Dust clouds of equal mass of crocidolite remain airborne for longer time periods than those of amosite of equal mass and similarly amosite clouds of equal mass remain airborne for longer than anthophyllite clouds of equal mass which means that in such clouds of equal mass the number of respirable fibers will be largest for crocidolite and least for anthophyllite. Chrysotile tends to subdivide more finely into much finer fibrils but this depends to a large extent on the degree of processing and so its respirability may be similar to that of the amphiboles in some circumstances. Fiber diameter, length and straightness (flexibility) are all factors in determining the depth of penetration.

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~~The work of Stanton and others~~ Experimental evidence indicates that fibers other than asbestos may be able to produce ~~pleural~~ mesothelioma after being placed in the pleural cavities or peritoneal cavities of animals. (25) It has been shown that this will only occur if the fibers are of a certain diameter and length. The carcinogenicity of fibers appears to be related to their size and shape and for asbestos, glass fiber

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a real fear expressed by some investigators.[35]

Apart from the role of the pathologist

In addition to the pathologists' diagnostic role another important factor exposure indicator can be determined as a result of a carefully conducted evaluation of available tissue from autopsy material or surgical material, namely, the presence the detection of asbestos bodies and an estimation of their numbers.[36] Autopsy and resected material ~~was~~ ~~have been~~ examined for the presence of asbestos bodies and the distribution of the quantities found suggested that almost everyone in the population studied had had some exposure to asbestos but that certain persons were subject to an additional occupational exposure.[37] In a prospective study of lung tissue from mesothelioma cases and controls in ~~the~~ Britain it was found that mesothelioma patients had more amphibole fibers in their lungs than did control cases, chrysotile fibers were not present in greater numbers in the mesothelioma patients than in the control cases, and 30 of the 93 cases studies had no chrysotile fibers in their lungs.[38] Using a technique for digesting lung tissue with 'potash' and examining the preparation with phase-contrast microscopy, the light-visible asbestos-fiber content of 300 lung specimens was measured by Wagner et al[39] in Britain, and the results were correlated with the occupations of the patients. ~~In 100 cases~~ 95% ~~mesothelioma~~ of the patients with mesothelioma had more than 50,000 asbestos fibers per gram of dried lung in the base of a lower lobe, whereas only 15% of the control series had as much asbestos. Lungs from 100 patients with lung cancer but no industrial disease contained less than 20,000 fibers per gram of dried lung in 80% of ca.

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The number of asbestos fibers found in the lungs was closely related to the occupations of the patients but not to their home environment (ie geographic location). Patients who had lived near likely sources of atmospheric asbestos pollution did not have higher asbestos fiber counts than the rest of the patients. This last study provides additional evidence that the development of asbestos-related mesothelioma is dose related, an encouraging result in the evaluation and control of risk in the general environment.

When the reported measurements of ambient air reported in the literature are studied (39) we see that even the highest figure for contamination of the general atmosphere is three orders of magnitude below the current hygiene standard for asbestos. In considering the risk factors involved in mesothelioma incidence ~~are~~ is the effects of changes in processing, marketing and usage of asbestos products over the time period studied should not be ignored. There has been continuous improvement in dust control in most workplaces where asbestos is used (39)(40) and, therefore, a decreasing emission of dust from these sources. The emission of fibers from brake linings has been cited as a source of asbestos in ambient air (40)(41) and some observers report that this raises the background level where traffic is dense and where brakes are applied such as at toll booths or traffic intersections. There is still some controversy as to whether modern brakes emit fibers in significant amounts and according to one report most asbestos emitted from vehicle brakes and clutches is converted to other products, with only 3.2% of total asbestos emitted entering the atmosphere.(42) Data reported in 1971 and 1972 related to large

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vehicles containing almost exclusively asbestos-based friction materials. Today's cars are smaller and have smaller brakes, so that they use less total weight of asbestos. More important, in 1979 and 1980, approximately 40% and 50% respectively, of the front brakes on passenger cars and light trucks have non-asbestos semi-metallic disc pads. This again is a reduction in the use of asbestos in automotive friction materials.(43) These changes will of course not have any direct bearing on cases studied retrospectively but should be carefully considered in prospective studies in the future.

retrospective

In a study of cases of mesothelioma from a major urban hospital in the USA, of the 36 cases on file, 19 were not associated with asbestos exposure.(44) The authors of this study found that the lack of history of exposure correlated with postmortem histology by light microscopy. " When postmortem material was reviewed, evidence of asbestos exposure was present in all cases of mesothelioma with a history of exposure to asbestos, and in no cases in which the patient denied a history of asbestos exposure."

An interesting study was conducted in South Africa where 70 consecutive patients suffering from mesothelioma of the pleura were interviewed to obtain confirmation of exposure to asbestos fibes.(45) Interviews were repeated at least once. " This was necessary to give the patient an opportunity to think over the details and environmental aspects of his working career." The authors were unable to obtain

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a history of asbestos exposure in only one of the 70 patients. The authors do not describe their interview technique or whether they used a standardized questionnaire and this study must be regarded as being biassed due to the effect of "pestering" a sick patient and pressing for a recollection of an event which conceivably occurred thirty or forty years previously. This study, although potentially significant in establishing a strong association between asbestos exposure and mesothelioma, requires to be more fully documented by the authors to eliminate numerous biases introduced by the selection of cases, interview techniques and lack of control cases.

The review of the problems related to the study of mesothelioma incidence indicates that the major difficulties encountered relate to the adequacy of exposure records and occupational histories, errors in diagnosis and lack of ~~knowledge of the role of~~ ability to quantify low-level environmental exposures to asbestos in a standardized manner which would enable dose relationships to be analyzed. Retrospective studies on mesothelioma incidence suffer from a common problem in due to lack of the above information. It is even possible that because awareness of the association between mesothelioma and asbestos exposure has increased dramatically in the past decade in the medical, legal and general communities, the diagnostic frequency has been falsely elevated and influenced estimates of disease prevalence or incidence in ~~the~~ industrial populations. Furthermore, prior to the "time of increased awareness", many cases could conceivably have been misdiagnosed as other conditions and this would have resulted in a loss of information and underestimate of disease prevalence or incidence.

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